REMARKS

In the Office Action dated February 15, 1990, the Examiner withdrew claims 1-9 as directed to a non-elected invention. Pursuant to a teleconference with the Examiner held on February 27, 1990, claims as amended above are presented. Applicants submit that this amendment obviates the Examiner's objection, in that claims 1-9 as amended are drawn to the invention originally claimed.

Support for the recitation of the amended claims, "plurality of viable human neonatal or fetal hematopoietic stem cells derived for the blood" occurs throughout the instant specification, as exemplified e.g. by the recitation on page 20, lines 16-17 ("the present invention relates to the use of fetal or neonatal stem cells..."); page 24, lines 30-31 ("Fetal or neonatal blood are sources..."); page 27, lines 26-29 ("hematopoietic stem and progenitor cells can potentially be multiplied in culture, before or after cryopreservation...,thus expanding the number of stem cells..."); page 42, lines 1-3 ("Doubtless, under clinical conditions in man it would generally require more than a single stem cell to rescue the hematopoietic system.").

The Examiner has also cited Rinfret et al. to show that it is conventional to add cryoprotectants to blood prior to freezing. The Examiner adds that it would be obvious to add cryoprotectants to hematopoietic stem cells prior to freezing following the teaching of Rinfret et al. Applicants respectfully point out, that, even assuming arguendo that the Examiner's contentions were correct, the claimed invention is not in any way rendered obvious, since the claimed invention is directed to cryopreserved human neonatal/fetal stem cells of the blood. As clearly set forth in the instant specification, Applicants discovered the utility of

cryopreserved human neonatal/fetal blood stem cells for hematopoietic reconstitution. There is no hint or suggestion in the prior art of cryopreserved hematopoietic stem cells from human fetal or (neonatal) cord blood. The use of such human neonatal/fetal blood stem cells is clearly nonobvious. As pointed out in the instant specification on p. 23, neonatal blood obtained from the umbilical cord and placenta is customarily discarded at birth! Such neonatal/fetal blood was deemed in the prior art to be so lacking in utility that it was routinely discarded. It was not until Applicants' invention that the utility of such blood cells, in combination with a cryopreservative, was recognized.

Furthermore, considering the secondary indicia of nonobviousness, e.g., In re Sernaker, 227 U.S.P.Q. 1 (Fed. Cir. 1983); In re Imperata, 179 U.S.P.Q. 730 (C.C.P.A. 1973), Applicants contend that the long felt need for effective, safely and easily obtainable compositions for use in hematopoietic reconstitution, and the difficulties encountered with compositions disclosed in the prior art for use in hematopoietic reconstitution, provide further proof of the nonobviousness of the instant invention.

As discussed in Section 2 of the instant specification, some years prior to the filing of the above-identified application, there existed recognition in the art that successful hematopoietic reconstitution would be valuable in the treatment or prevention of many diseases and disorders. As summarized in Section 2.2, pp. 9-12 of the instant specification, bone marrow, adult peripheral blood, fetal liver, neonatal spleen, and neonatal thymus have been investigated as possible sources of stem cells for hematopoietic reconstitution. However, there are drawbacks to each of the prior art systems that had been investigated

as possible sources of stem cells for hematopoietic reconstitution at the time of filing the above-identified application. With respect to bone marrow, as stated on p. 25, lines 13-15 of the specification, bone marrow collection is an invasive, traumatic procedure, thus posing some risk to the donor, and is expensive and laborious. Furthermore, with respect to attempted autologous hematopoietic reconstitution, bone marrow transplantation entails many disadvantages not encountered with use of neonatal cells, including the sick or suboptimal condition of the donor. As stated on p. 10, line 23 through p. 11, line 15 of the instant specification:

> Present use of bone marrow transplantation is severely restricted....Even in such an autologous system, the danger due to undetectable contamination with malignant cells, and the necessity of having a patient healthy enough to undergo marrow procurement, present serious limitations. [references omitted]

In contrast, in the use of neonatal or fetal cells as provided by the present invention, neonatal blood that is otherwise discarded is readily obtainable for use without risk to the donor.

The Examiner's attention is further directed to the following description of additional long-desired advantages supplied by the use of human neonatal/fetal blood cells:

> Furthermore, the prospects of success in bone marrow transplantation decline with age; although it is not clear whether the age of donor or patient is more important, it is proper to infer that younger (neonatal) cells are preferable for hematopoietic reconstitution. Such neonatal or fetal cells have not been subjected to the "environmental outrage" that adult cells have undergone. Also, as an example of novel medical applications which may be feasible with neonatal cells but not with conventional bone marrow transplantation, restoration with self cells taken at birth can be valuable in the treatment of disorders such as declining immune

> responsiveness and autoimmunity (immune reactions against one's own tissues) which occur in increasing frequency with age.
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> ...
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> There are additional reasons for preferring the use of neonatal cells for hematopoietic reconstitution as provided by the present invention. Neonatal blood is a preferred source of cells for hematopoietic reconstitution, since it is free from viral and microbial agents, known or unknown, latent or otherwise, that may be encountered in later life, other than those transmitted from the mother or during labor and delivery. In addition, in view of the extent to which the hematopoietic stem cell may possibly share with other cells the limitation in total number of cell divisions that is may undergo before senescence, it is proper to assume that the neonatal hematopoietic stem cell has a self-renewal and reconstituting capacity that is at least as great, and perhaps greater, than that of hematopoietic stem cells obtained at any later time in life.
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> In adults, stem and progenitor cells are mostly confined to the bone marrow; very few circulate in the blood. In the newborn human or animal, however, stem and progenitor cells circulate in the blood in numbers similar to those found in adult bone marrow. Doubtless this reflects the great demands for blood formation of the growing infant. We calculate that the restorative capacity of neonatal blood contained in the human umbilical cord and placenta, which are customarily discarded at birth, equals or exceeds that of the average donation of an adult's bone marrow. (instant specification at p. 22, lines 5-18, and p. 23, lines 3-27).

With respect to the use of adult peripheral blood cells, it appears that while in some studies promising results have been obtained for patients with various leukemias and with lymphoma, other studies using peripheral blood have failed to effect reconstitution (see, for example, Hersko et al., 1979, the Lancet 1.:945-947, reference AT of record). Additionally, the collection of peripheral blood can be time consuming and uncomfortable. Furthermore:

> Many of the relative disadvantages discussed supra of the use of bone marrow cells for hematopoietic reconstitution [disadvantages due to age], also apply to the use of adult peripheral blood for such reconstitution, and thus, the use of neonatal cells for hematopoietic reconstitution according to the present invention provides distinct advantages over the employment of adult peripheral blood. (instant specification at p. 22, lines 19-25)

There are also numerous difficulties in using blood obtained from fetal liver, neonatal spleen, and fetal and neonatal thymus. Firstly, only limited success has been obtained in studies using fetal liver or fetal thymus transplants (see Ochs et al., 1981, Pediatr. Res. 15 (4 part 2):601, reference BH of record; and Touraine et al., 1983, Birth Defects 19(3):139-142, reference BL of record). Applicants further point out to the Examiner the difficulty in obtaining fetal liver or other organ samples.

In contrast, the compositions of the present invention supply a long-felt need for useful, safely and easily obtainable sources of hematopoietic stem and other cells useful for hematopoietic reconstitution. The neonatal/fetal blood cells can easily be obtained from umbilical cord blood available on delivery of the donor baby, and cryopreserved for later use. Specifically, cord blood can be obtained by direct drainage from the cord and/or by needle aspirations from the delivered placenta at the root and at distended veins. Therefore, cord blood can be obtained without trauma to the donor, easily and inexpensively. The Applicants further point out that many difficulties had been experienced in obtaining hematopoietic reconstitution using methods known in the prior art. In contrast, as disclosed in the Declaration under 37 C.F.R.

§1.132 by Hal E. Broxmeyer submitted with the Amendment filed September 5, 1989, the compositions of the present invention have been used to carry out the successful reconstitution of the hematopoietic system, in a patient with Fanconi's anemia.

The Applicants conclude that the claimed compositions fulfill a long felt need for an easily accessible source for stem and other blood cells that can be used for hematopoietic reconstitution in patients with various diseases and disorders. Consideration of the secondary criteria for nonobvious clearly evidences the nonobviousness of the instant invention.

The amendments and remarks made herein are not to be construed as an admission by Applicants of concurrence with the Examiner's withdrawal of the claims in the Office Action dated February 15, 1990, or a waiver of any objection thereto. Applicants reserve the right to petition from the withdrawal of the claims.

Applicants respectfully request the entry of the foregoing amendments and remarks into the file of the above-captioned application. An allowance of the claims is earnestly requested.

Additionally, Applicants again note that they have not received the revised Form PTO 1449 initialled by the Examiner, which was filed with the Supplemental Information Disclosure Statement on September 5, 1989.

Respectfully submitted,

PENNIE & EDMONDS
Attorneys for Applicants

Dated: 3-13-90
Tel. (212) 790-9090

By Adrianne Antler Reg. No. 32,605
S. Leslie Misrock
(Reg. No. 18,872)